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Corticosteroid use prevents primary *Clostridioides difficile* infection in the setting of broad-spectrum antibiotic use among hospitalized patients

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ABSTRACT

Background. *Clostridioides difficile* is the most common pathogen causing healthcare-associated infections in the U.S. and a Centers for Disease Control and Prevention urgent threat level pathogen. The pathophysiology of *C. difficile* infection (CDI) involves neutrophil invasion of the colon associated with an inflammatory response. Previous case-control studies investigating an anti-inflammatory corticosteroid (CS) effect on CDI risk demonstrated conflicting results but were unable to control for antibiotic use. We hypothesized that CS use would decrease the risk of CDI in a well-matched, high-risk population.

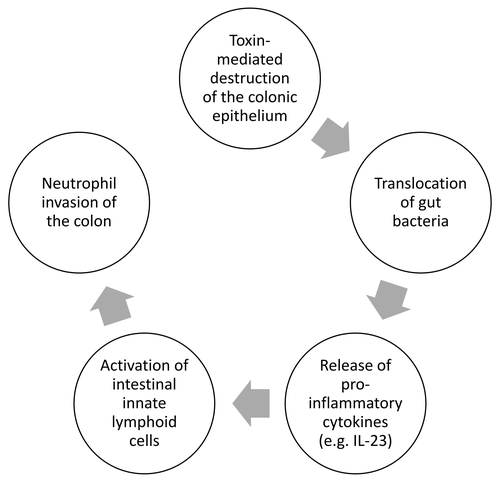
Methods. This nested case-control study included hospitalized patients admitted to a single quaternary care hospital in the Texas Medical Center. The case population included adults who were diagnosed with CDI and received at least one dose of an antibiotic of interest (cefepime, meropenem, or piperacillin-tazobactam) in the 90 days prior to CDI diagnosis. The control population included hospitalized adults who received one of the same antibiotics during their hospital stay but did not develop CDI in the 90 days following their first dose. Patients were excluded if they had a documented history of CDI. CS use was defined as ≥ 20 mg prednisone or equivalent administered in the 48 hours prior to CDI diagnosis (cases) or antibiotic start (controls). The primary study outcome was the development of CDI. A logistic regression model was developed modeling CDI diagnosis as a function of available patient covariates.

Results. A total of 321 patients met the inclusion criteria; 56 patients had a history of CDI, leaving a final study cohort of 265 patients (104 cases and 161 controls). Antibiotic days of therapy were significantly higher in the control group (8 vs. 6 days; P = 0.02). The odds of CDI diagnosis were lower among patients administered CS (OR, 0.17; 95% CI, 0.08-0.38; P < 0.001), which remained protective in the multivariable model after adjusting for age, gender, and invasive GI surgery within six months.

Conclusions. We observed an association between CS use and decreased risk of developing primary CDI in hospitalized patients receiving broad-spectrum antibiotics. Future studies are needed to delineate the dose and duration of CS needed to realize this effect.

BACKGROUND

Figure 1. *C. difficile* infection (CDI) pathophysiology



- An overactive immune response can have a detrimental effect on a host with CDI
- A number of case-control studies have suggested corticosteroid (CS) use increases a patient's risk of developing CDI, while others have found it to be protective against the development of CDI
- Prior studies have a number of limitations:
  - lack of control for antibiotic use
  - lack of CS dosing documentation
  - changes in diagnostic testing over time
  - populations that limit generalizability

SPECIFIC AIM

To assess the effect of CS use on the development of CDI using univariate and multivariable analysis

METHODS

Study design

Nested case-control study

Inclusion criteria

Cases	Controls
Administered at least one dose of an antibiotic of interest	
Diagnosed with CDI	Did not develop CDI in the 90 days following their first dose of antibiotic

Exclusion criteria

Documented history of CDI

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Definitions

- **Antibiotic of interest**: cefepime, meropenem, or piperacillin-tazobactam
- **Antibiotic days of therapy (DOT):** an aggregate sum of days for which any amount of an antibiotic of interest was administered
- **CS use**: ≥ 20 mg prednisone or equivalent

Statistical analysis

- **Baseline characteristics**
  - Binary/categorical variables: $\chi 2$ or Fisher's exact test
  - Continuous variables: Student's t-test or Wilcoxon rank-sum test
- **Primary outcome:** CDI diagnosis
  - Univariate and multivariable logistic regression analysis

RESULTS

Table 1. Comparison of patient characteristics between cases and controls

Covariate	Cases (n = 104)	Controls (n = 161)	P value
Age, mean (±SD), y	63.5 (16.8)	66.5 (12.9)	0.10
Female, no. (%)	53 (51.0)	62 (38.5)	0.05
CCI, median (IQR)	2 (1-4)	3 (1-5)	0.30
SOT, no. (%)	8 (7.7)	26 (16.2)	0.04
Residence PTA, no. (%)			
Home	78 (75.0)	120 (74.5)	0.93
Recent GI surgery, no. (%)	15 (14.4)	46 (28.6)	0.01
Steroid use, no. (%)	8 (7.7)	53 (32.9)	<0.001
PPI use, no. (%)	72 (69.2)	106 (65.8)	0.57
Zolpidem use, no. (%)	6 (5.8)	11 (6.8)	0.73
Antibiotic use, no. (%)			
Cefepime	67 (64.4)	61 (37.9)	<0.001
Meropenem	41 (39.4)	66 (41.0)	0.80
Piperacillin-tazobactam	49 (47.1)	59 (36.7)	0.09
Antibiotic DOT, median (IQR)	6 (3-10)	8 (4-13)	0.02

Table 2. Univariate and multivariable analysis for predictors of *Clostridioides difficile* infection

Covariate	Univariate analysis OR (95% CI)	P value	Multivariable analysis OR (95% CI)	P value
Steroid use	0.17 (0.08-0.38)	<0.001	0.14 (0.06-0.32)	<0.001
PPI use	1.17 (0.69-1.98)	0.57		
Ambien use	0.83 (0.30-2.33)	0.73		
Age	0.99 (0.97-1.00)	0.10	0.98 (0.96-0.99)	0.02
Female	1.65 (1.01-2.73)	0.05	1.84 (1.07-3.16)	0.03
CCI	0.93 (0.84-1.02)	0.13		
SOT	0.43 (0.19-1.00)	0.05		
Recent GI surgery	0.42 (0.22-0.80)	0.01	0.33 (0.17-0.66)	0.002
Residence home	1.03 (0.58-1.81)	0.93		
Antibiotic DOT	0.96 (0.93-0.99)	0.02		

Table 3. Stratified analysis of cases by corticosteroid use

Covariate	Steroids (n = 8)	No steroids (n = 96)	P value
Age, mean (±SD), y	60.9 (10.4)	63.7 (17.3)	0.65
Female, no. (%)	2 (25.0)	51 (53.1)	0.16
CCI, median (IQR)	2.5 (1.5-4.5)	2 (1-4)	0.54
SOT, no. (%)	3 (37.5)	5 (5.2)	0.01
Residence PTA, no. (%)			
Home	5 (62.5)	73 (76.0)	0.41
Recent GI surgery, no. (%)	0 (0.0)	15 (15.6)	0.60
PPI use, no. (%)	5 (62.5)	67 (69.8)	0.70
Zolpidem use, no. (%)	1 (12.5)	5 (5.2)	0.40
Antibiotic use, no. (%)			
Cefepime	3 (37.5)	64 (66.7)	0.13
Meropenem	0 (0.0)	41 (42.7)	0.02
Piperacillin-tazobactam	6 (75.0)	43 (44.8)	0.14
Antibiotic DOT, median (IQR)	7 (4-8.5)	6 (3-10.5)	0.97
Albumin, mean (±SD), g/dL	3.0 (0.7)	2.8 (0.6)	0.47

CONCLUSION

Corticosteroid use significantly reduced the odds of developing CDI in a cohort of hospitalized patients without a history of CDI who received cefepime, meropenem, or piperacillin-tazobactam.